IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: ALLAN and KELLEY Application No.: 10/734,625 Filed: December 15, 2003 For: **Lipoxygenase Inhibitors as Hypolipidemic and Anti-Hypertensive Agents**	Confirmation No.: 2541 Art Unit: 1612 Examiner: FAY, Zohreh A. Atty. Docket: 1633.0400002/PAJ/GAL

Brief on Appeal Under 37 C.F.R. § 41.37

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Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

A Notice of Appeal from the final rejection of claims 1, 4, 5, 8, 9 and 14-17 was filed on December 10, 2008. Appellants hereby file this Appeal Brief together with the required fee set forth in 37 C.F.R. § 41.20(b)(2). An Evidence Appendix containing Exhibits 1-7 follows page 30 of this paper.

It is not believed that extensions of time are required beyond those that may otherwise be provided for in documents accompanying this paper. However, if additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required therefor (including fees for net addition of claims) are hereby authorized to be charged to our Deposit Account No. 19-0036.

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I. Real Party in Interest (37 C.F.R. § 41.37(c)(1)(i))

The real party in interest in this Appeal is Insmed, Incorporated ("Insmed"), the Assignee of record. Insmed is the Assignee of the present invention by virtue of an Assignment from the Inventors to Insmed, executed on May 5, 2004 and recorded against the present application on May 14, 2004, beginning at reel 014610/frame 0264. A Corrective Assignment to replace the Assignor's recorded name of "Glen Kellely" with "Glen Kelley" was recorded against the present application on May 27, 2004, beginning at reel 014673/frame 0440.

II. Related Appeals and Interferences (37 C.F.R. § 41.37(c)(1)(ii))

There are no prior or pending Appeals, Interferences or judicial proceedings known to Appellants, the Appellants' legal representative, or Assignee which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the present Appeal.

III. Status of Claims (37 C.F.R. § 41.37(c)(1)(iii))

Claims 1, 4, 5, 8, 9 and 14-17 are pending and rejected. Claims 6, 7 and 10-13 are pending and withdrawn. Claims 2 and 3 are cancelled.

In the Office Action mailed April 9, 2007, the Examiner requested an election of a single species of 5-lipoxygenase inhibitor. In the Reply to Requirement for Election of Species dated April 30, 2007, Applicants provisionally elected phenyl pyrazoline derivatives with traverse. In the Office Action mailed July 26, 2007, the Examiner withdrew claims 6, 7 and 10-13 and examined the elected species of phenyl pyrazoline derivatives. As such, Appellants will address claims 1, 4, 5, 8, 9 and 14-17 in this Appeal Brief to the extent that the Examiner has examined the elected species, although some of claims 1, 4, 5, 8, 9 and 14-17, as presently worded, include other species.

Claims 2 and 3 were cancelled and claim 1 was amended in the Amendment and Reply Under 37 C.F.R. § 1.116 dated September 10, 2008. The Advisory Action mailed November 14, 2008 indicates that the September 10, 2008 Amendment and Reply will be entered for the purposes of appeal.

Claims 1, 4, 5, 8, 9 and 14-17 are on appeal.

IV. Status of Amendments (37 C.F.R. § 41.37(c)(1)(iv))

Claims 2 and 3 were cancelled and claim 1 was amended in the Amendment and Reply Under 37 C.F.R. § 1.116 dated September 10, 2008. The Advisory Action mailed November 14, 2008 indicates that the September 10, 2008 Amendment and Reply will be entered for the purposes of appeal.

V. Summary of Claimed Subject Matter (37 C.F.R. § 41.37(c)(1)(v))

Claim 1 is the sole independent claim involved in this appeal. Claim 1 is directed to a method for treating elevated serum triglycerides comprising administering to a human subject with elevated serum triglycerides an effective amount of a pharmaceutical composition comprising a 5-lipoxygenase inhibitor, said effective amount being sufficient to reduce said elevated serum triglycerides, wherein said 5-lipoxygenase inhibitor is not nordihydroguaiaretic acid (NDGA) or curcumin. Claims 4, 5, 8, 9 and 14-17 depend, either directly or indirectly, from claim 1, and specify the following:

the pharmaceutical composition is an oral dosage form (claim 4);

the 5-lipoxygenase inhibitor is selected from the group consisting of an acetohydroxamic acid derivative, a phenyl pyrazoline derivative, a 2-(12-hydroxydodeca-5,10-diynyl)-3,5,6-trimethyl-1,4-benzoquinone derivative, and a 3-[1-(4-chlorobenzyl)-3-t-butyl-thio-5-isopropylindol-2-yl]-2,2-dimethyl propanoic acid derivative (claim 5);

the 5-lipoxygenase inhibitor is a phenyl pyrazoline derivative (claim 8);

the phenyl pyrazoline derivative is 4,5-dihydro-1-(3-(trifluoromethyl)phenyl)-1H-pyrazol-3-amine (BW 755c) (claim 9);

the effective amount of the 5-lipoxygenase inhibitor is between 0.1 μg and 500 mg per kilogram of body weight (claim 14);

the effective amount of the 5-lipoxygenase inhibitor is between 0.5 mg to 500 mg per kilogram of body weight (claim 15);

the method further comprises administering a second compound selected from the group consisting of anti-diabetic compounds, lipid-lowering medications and anti-hypertensive compounds (claim 16)[1]; and

the method further comprises concurrent administration of the 5-lipoxygenase inhibitor and a second compound selected from the group consisting of anti-diabetic compounds, lipid-lowering medications and anti-hypertensive compounds (claim 17)[2].

Claims 1, 4, 5, 8, 9 and 14-17 are supported throughout the specification, *e.g.*, as exemplified by Table 1:

Table 1: Illustrative Support in the Specification for the Pending Claims

Claim No.	Illustrative Support from the Specification
1	p. 4, lns. 17-22; p. 31, lns. 2-7; p. 8, lns. 19-21
4	p. 14, lns. 7-11; p. 14, lns. 23-41; p. 15, ln. 1- p. 16, ln. 8; p. 31, lns. 11-12
5	p. 4, lns. 23-30; p. 31, lns. 13-17
8	p. 9, lns. 1-4; p. 31, lns. 22-23
9	p. 9, lns. 1-5; p. 18, lns. 23-25; p. 24, Table 2, "HFF+BW755"; Figure 1, "BW-755c 100mg/kg bid"; Figure 2B, upper panel, "BW-755c" and "BW-755c-5"; p. 32, lns. 1-3
14	p. 12, ln. 27- p. 13, ln. 2; p. 32, lns. 15-17
15	p. 12, ln. 27- p. 13, ln. 6; p. 32, lns. 18-20
16	p. 10, lns. 12-19; p. 32, ln. 21- p. 33, ln. 2
17	p. 10, lns. 12-19; p. 7, lns. 21-27; p. 32, lns. 3-4

[1] It has come to the Appellants' attention that claim 16 contains the following obvious typographical error: "hyptertensive" should read "hypertensive." As such, Appellants will address claim 16 in this Appeal Brief as if it were in the corrected form.

[2] It has come to the Appellants' attention that claim 17 contains the following obvious typographical error: "claim 14" should read "claim 16." As such, Appellants will address claim 17 in this Appeal Brief as if were in the corrected form.

VI. Ground of Rejection To Be Reviewed on Appeal (37 C.F.R. § 41.37(c)(1)(vi))

The sole ground of rejection to be reviewed on Appeal is whether claims 1, 4, 5, 8, 9 and 14-17 are obvious under 35 U.S.C. § 103(a) over Gowri *et al.*, *Am. J. Hypertens.* 12: 744-746 (1999)("Gowri 1999," copy attached hereto as Exhibit 1) and Gowri *et al.*, *Am. J. Physiol. Endocrinol. Metab.* 279: E593-E600 (2000)("Gowri 2000," copy attached hereto as Exhibit 2), in view of U.S. Patent No. 4,572,913 to Copp *et al.* ("Copp," copy attached hereto as Exhibit 3).

VII. Arguments (37 C.F.R. § 41.37(c)(1)(vii))

A. The Claimed Methods Are Not Obvious Over the Cited Art

i. Legal Principles Related to Obviousness

Obviousness determinations under 35 U.S.C. § 103 are carried out according to the standard set forth by the United States Supreme Court in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 148 U.S.P.Q. (BNA) 459 (1966):

> [u]nder § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or nonobviousness, these inquiries may have relevancy.

Id. at 17-18, 148 U.S.P.Q. at 467.

In proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. *See In re Piasecki,* 745 F.2d 1468, 1471-73, 223 U.S.P.Q. 785, 787-788 (Fed. Cir. 1984). Examiners, following then-existing Federal Circuit precedent, traditionally had the burden of demonstrating that all of the claim limitations were taught or suggested in a

prior art reference or a combination of references, and further that the references themselves or the knowledge generally available to one of ordinary skill in the art, provided some suggestion or motivation, either to modify a reference or to combine the references in order to arrive at the claimed invention with a reasonable expectation of success. *See generally In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442-1443 (Fed. Cir. 1991). This analysis has come to be known as the "teaching-suggestion-motivation" ("TSM") test.

The U.S. Supreme Court reviewed and restated its obviousness jurisprudence originally established over forty years ago in *Graham*. *See KSR International Co. v. Teleflex, Inc.*, 550 U.S. 398, 127 S.Ct. 1727, 82 U.S.P.Q.2d 1385 (2007). In *KSR*, the Court determined that the Federal Circuit had been too rigid in *requiring* use of the TSM test to determine obviousness. Nonetheless, the Court recognized that TSM analysis could provide a helpful insight, emphasizing that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was independently known in the prior art." *Id.* at 1741, 82 U.S.P.Q.2d at 1396. Rather, there must be a reason or rationale behind an obviousness determination and "this analysis should be made explicit." *Id.* (citing *In re Kahn*, 441 F.3d 977, 988, 78 U.S.P.Q.2d (BNA) 1329, 1336 (Fed. Cir. 2006) ("[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.")).

In response to *KSR*, the Office issued "Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co. V. Teleflex Inc.*" 72 Fed. Reg. 195, pp. 57526-35 (October 10,

2007)("Guidelines"). The Guidelines reiterate and emphasize the Examiner's role as a factfinder, using the factual inquiries set forth in *Graham*. Based on the fact record, the Examiner must use "articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." Guidelines at 57529 col. 1 (internal citation omitted).

The Guidelines present several rationales which may be used by an Examiner to reject a claimed invention as obvious, one of which is the familiar TSM test. Common to all the rationales is the requirement for the Examiner to demonstrate, based on the *Graham* factual inquiries, that a person of ordinary skill in the art *would*, as of the filing date, have recognized that the claimed invention, as a whole, was predictable, or would have enjoyed a reasonable expectation of success. Guidelines at 57529, col. 1.

ii. Scope and Content of the Prior Art

1. Gowri 1999

Gowri *et al.*, *Am. J. Hypertens*. 12: 744-746 (1999)("Gowri 1999," copy attached hereto as Exhibit 1) provides experimental results correlating the treatment of rats with fructose-induced hypertension with the lipoxygenase inhibitor masoprocol (nordihydroguaiaretic acid or NDGA) and the reduction of systolic blood pressure, plasma insulin, free fatty acid and triglyceride concentrations. *See* Gowri 1999 at p. 744, abstract; p. 745, left col., lns. 51-55; and p. 745, right col. Table 1. According to the authors, "the mechanistic explanation for the hemodynamic and metabolic effects of masoprocol documented in this study are not self-evident." Gowri 1999, p. 746. left col., lns. 7-9. The authors provide a possible mechanistic explanation for these effects, speculating that "masoprocol increases insulin sensitivity in fructose-fed rats, thereby leading to a concomitant decrease in blood pressure and plasma insulin and triglyceride concentrations." Gowri 1999, p. 746, left col., lns. 14-18. However, the authors also

propose the hemodynamic and metabolic effects observed with masoprocol treatment may be caused by masoprocol's effects on magnesium metabolism or by masoprocol's actions as an antioxidant. *See* Gowri 1999, p. 746, left col., lns. 21-28 and lns. 37-39 (stating, for example, "[o]n the other hand, as masoprocol is also an antioxidant, this alternative mechanism of action cannot be excluded").

Gowri 1999 does not teach phenyl pyrazoline derivatives and does not attribute the action of masoprocol to 5-lipoxygenase inhibition.

2. Gowri 2000

Gowri *et al.*, *Am. J. Physiol. Endocrinol. Metab.* 279: E593-E600 (2000)("Gowri 2000," copy attached hereto as Exhibit 2) provides experimental results correlating the anti-lipolytic activity of masoprocol with the inhibition of adipose tissue hormone-sensitive lipase (HSL) phosphorylation. *See* Gowri 2000 at p. E593, abstract; p. E593, left col., lns. 51-55; and p. 745, right col., Table 1. According to Gowri 2000, "[a]lthough a well known lipoxygenase inhibitor, the profound metabolic effects of masoprocol only recently became apparent. The possibility that these effects may not be mediated by the lipoxygenase pathway must be considered, given the observation that esculetin, another lipoxygenase inhibitor, had no anti-lipolytic activity." Gowri 2000, p. E599, left col., ln. 60- right col., ln. 5 (internal citation removed).

Gowri 2000 does not teach phenyl pyrazoline derivatives and does not attribute the action of masoprocol to 5-lipoxygenase inhibition.

3. Copp

The Examiner has conceded that Gowri 1999 and Gowri 2000 differ from the claimed invention in the "use of the claimed li[p]oxygenase inhibitor, a phenyl

pyrazoline derivative," and cites U.S. Patent No. 4,572,913 to Copp *et al.* ("Copp," copy attached hereto as Exhibit 3) as teaching the use of phenyl pyrazoline derivatives as a lipoxygenase inhibitor. *See, e.g.*, Office Action mailed January 9, 2008, p. 2, lns. 18-20.

Copp describes the use of certain phenyl pyrazoline derivatives in the prophylaxis or treatment of inflammation, pain, pyresis and asthma. *See* Copp, col. 7, lns. 7-23. Copp does not teach the inhibition of 5-lipoxygenase or the treatment of elevated serum triglycerides.

4. Scribner

Scribner *et al.*, *Metabolism* 49(9): 1106-1110 (2000)("Scribner," copy attached hereto as Exhibit 4) provides further experimental results correlating the treatment of rats with fructose-induced hypertriglyceridemia with masoprocol and reduced serum triglyceride concentrations. Scribner does not teach phenyl pyrazoline derivatives and does not attribute the action of masoprocol to 5-lipoxygenase inhibition.

5. Nadler

U.S. Patent No. 6,191,169 B1 to Nadler *et al.* ("Nadler," copy attached hereto as Exhibit 5) describes the role of 12-lipoxygenase inhibitors in the pathogenesis of diseases including atherosclerosis, breast cancer, autoimmune, inflammatory disease, diabetic vascular and kidney disease, and insulin resistance. Nadler does not describe hypolipidemic properties of lipoxygenase inhibitors. Nadler does not teach phenyl pyrazoline derivatives and does not attribute the action of masoprocol to 5-lipoxygenase inhibition.

iii. Summary of the Office's Basis for the Obviousness Rejection

The Examiner asserted that Gowri 1999 teaches the "use of masoprocol, a li[p]oxygenase inhibitor for the lowering [of] blood pressure." Office Action mailed

January 9, 2008, p. 2, lns. 15-16. The Examiner further asserted that Gowri 2000 teaches that "masoprocol, a li[p]oxygenase inhibitor lowers serum triglycerides in rats." *Id.* at p. 2, lns. 16-17. The Examiner has conceded that Gowri 1999 and Gowri 2000 differ from the claimed invention in the "use of the claimed li[p]oxygenase inhibitor, a phenyl pyrazoline derivative." *Id.* at p. 2, lns. 18-19. However, the Examiner cited Copp to teach "the use of phenyl pyrazoline derivatives as lipoxygenase inhibitors." *Id.* at p. 2, lns. 19-20. The Examiner concluded that it would have been

> obvious to a person skilled in the art to use a phenyl pyrazoline for the treatment of hypertension and elevated blood triglycerides, motivated by the teachings of Copp et al., reference, which teaches phenyl pyrazole derivatives as lipoxygenase inhibitors.

Id. at p. 2, lns. 20-23.

With respect to the motivation to combine the art, the Examiner alleged that:

> [o]ne skilled in the art would have been motivated to combine the teachings of the above references, since Gowri et al. teach the use [of] a li[p]oxygenase inhibitor for treatment of hypertension and lowering serum triglyceride, and the other relates to the use of phenyl pyrazole derivatives as lipoxygenase inhibitor[s]. The substitution of one lipoxygenase inhibitor for another would have been obvious to a person skilled in the art in the absence of evidence to the contrary.

Id. at p. 2, ln. 24- p. 3, ln. 4.

iv. Claims 1, 4, 5, 8, 9 and 14-17 Are Not Obvious Over The Cited Art.

1. The Examiner Has Not Articulated With Particularity the Reasons to Support That One Skilled in the Art Would Have Substituted One Element For Another.

The United States Supreme Court in *KSR* has further clarified the requirements for obviousness analysis under 35 U.S.C. § 103(a) by noting that the analysis supporting

a rejection should be made *explicit*, and that it was "important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the [prior art] elements" in the manner claimed. The Court specifically stated:

> Often, it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was *an apparent reason* to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, *this analysis should be made explicit*. (*KSR*, slip opinion, page 14, *citing In Re Kahn*, 441 F. 3d 977,988 (CA, Fed. 2006) ([R]ejections on obviousness grounds *cannot be sustained by mere conclusory* statements, instead, there must be some articulated reasoning with some rational underpinning to support a legal conclusion of obviousness").

KSR at 1740-41, 82 U.S.P.Q.2d at 1396 (emphasis added).

Appellants assert that the Examiner has merely made conclusory statements and has failed to provide any articulated or explicit reasoning for combining the cited references to support an obviousness rejection. Specifically, in the Office Actions mailed on January 9, 2008 and on July 10, 2008 ("the Office Actions"), the Examiner has made the improper determination that masoprocol's status as a lipoxygenase inhibitor suggests that it would *only* act as a lipoxygenase inhibitor and, furthermore, that any effects masoprocol may have on rats would also hold true for other lipoxygenase inhibitors. As described above, Gowri 1999 and Gowri 2000 disclose that masoprocol has effects *outside* of the lipoxygenase pathway, and its use in lowering blood pressure and serum triglycerides in rats is not proven by the cited references to be elicited through the lipoxygenase pathway. The Examiner's reasoning to combine the "known" elements is that the "substitution of one lipoxygenase inhibitor for another would have been obvious to a person skilled in the art in the absence of evidence to the contrary." Office

Action mailed January 9, 2008, p. 3, lns. 2-4. Rejections on obviousness grounds cannot be sustained by such mere conclusory statements. As such, for at least this reason, Appellants respectfully request this rejection be withdrawn.

2. A Person of Ordinary Skill in the Art Would Not Have Found the Claimed Invention Predictable.

While the Office sets forth a number of rationales by which a determination of obviousness may be made (Guidelines at 57529), a common thread throughout requires that the prior art, in combination with the knowledge ascribed to the person of ordinary skill in the art, provide sufficient information to make the claimed invention fully and easily predictable. Appellants assert that a person of ordinary skill in the art would *not* have found the claimed invention predictable. As described above, Gowri 1999 does *not* establish masoprocol's lipoxygenase mechanism of action. Instead, Gowri 1999 *speculates* that the observed effects were because of masoprocol's lipoxygenase inhibitory activity. The authors declare "the mechanistic explanation for the hemodynamic and metabolic effects of masoprocol documented in this study are not self-evident." Gowri 1999, p. 746, lns. 7-9. Given the nature of the discussion by the authors, there is no indication of what compounds would work, or if the lipoxygenase pathway is even responsible for the observed effects. For example, the authors provide a possible mechanistic explanation by speculating that "masoprocol increases insulin sensitivity in fructose-fed rats, thereby leading to a concomitant decrease in blood pressure and plasma insulin and triglyceride concentrations." Gowri 1999, p. 746, lns. 14-18. The authors also propose that masoprocol could be eliciting an effect on magnesium metabolism or acting as an antioxidant. *See* Gowri 1999, p. 746, lns. 21-28 and lns. 37-39.

Even if the effects observed by masoprocol in Gowri 1999 and Gowri 2000 could have been attributable to inhibition of the lipoxygenase pathway, neither Gowri 1999 nor Gowri 2000 show evidence that it is attributable to *5-lipoxygenase* inhibition. Other types of lipoxygenase inhibition were known in the art at the effective filing date of the present application. For example, U.S. Patent No. 6,191,169 B1 to Nadler *et al.* ("Nadler," copy attached hereto as Exhibit 5) describes the role of 12-lipoxygenase inhibitors in the pathogenesis of diseases including atherosclerosis, breast cancer, autoimmune, inflammatory disease, diabetic vascular and kidney disease, and insulin resistance. Such a possibility only furthers the unpredictability of the claimed invention.

As further confirmed and explained in Gowri 2000, "[a]lthough a well-known lipoxygenase inhibitor, the profound metabolic effects of masoprocol only recently became apparent. The possibility that these effects may not be mediated by the lipoxygenase pathway must be considered, given the observation that esculetin, another lipoxygenase inhibitor, had no anti-lipolytic activity." Gowri 2000, p. E599, left col., ln. 60- right col., ln. 5 (internal citation removed). These comments provide further evidence that it was not understood at the time of the invention whether other lipoxygenase inhibitors would lower elevated levels of serum triglycerides or whether such possible effects on serum triglycerides were in fact mediated by the lipoxygenase pathway.

Neither Gowri reference shows that lipoxygenase inhibitors, acting through the 5-lipoxygenase pathway, act to lower serum triglycerides. The speculative nature of both Gowri references in linking the lipoxygenase pathway to masoprocol's observed effects and the observation of another (non-phenyl pyrazoline derivative) lipoxygenase inhibitor (esculetin) not having the same anti-lipolytic properties that masoprocol has would

certainly not rise to the level of providing predictability and motivating one skilled in the art to substitute one lipoxygenase inhibitor for another. As alleged by the Examiner, "[t]he substitution of one lipoxygenase inhibitor for another would have been obvious to a person skilled in the art *in the absence of evidence to the contrary*." Office Action mailed January 9, 2008, p. 3, lns. 2-4 (emphasis added). Appellants assert that Gowri 2000 provides such evidence to the contrary since esculetin, a lipoxygenase inhibitor, cannot be substituted for masoprocol, another lipoxygenase inhibitor, to lower lipolytic activity in rats. As such, for at least this reason, Appellants respectfully request this rejection be withdrawn.

3. There Is No Reasonable Expectation of Success in Combining Gowri 1999 and Gowri 2000 with Copp to Arrive at the Claimed Invention.

A prior art reference must be considered in its entirety, including portions that would lead away from the claimed invention. *See* M.P.E.P. § 2141.02(VI)(citing *W.L. Gore & Associates, Inc.* v. *Garlock*, Inc., 721 F.2d 1540, 220 U.S.P.Q. 303 (Fed. Cir. 1983)); *see also Panduit Corp. v. Dennison Mfg. Co.*, 774 F.2d 1082, 1093-94, 227 U.S.P.Q. 337, 340 (Fed. Cir. 1985)("The well established rule of law is that each prior art reference must be evaluated as an entirety...."). That is, "[t]here is no suggestion to combine...if a reference teaches away from its combination with another source." *Tec Air, Inc. v. Denso Manufacturing Michigan Inc.*, 192 F.3d 1353, 1360, 52 U.S.P.Q.2d 1294, 1296 (Fed. Cir. 1999); *see also KSR* at 1740, 82 U.S.P.Q.2d at 1397 (reaffirming "the corollary principle that when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious")(citing *United States v. Adams*, 383 U.S. 39, 51-52, 86 S.Ct. 708, 15 L.Ed.2d 572 (1966)). A reference teaches away "when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the

reference, *or would be led in a direction divergent from the path that was taken by the applicant*...." *In re Gurley*, 27 F.3d 551, 553, 31 U.S.P.Q.2d 1130, 1132 (Fed. Cir. 1994)(emphasis added).

Appellants submit that there is no reasonable expectation of success in combining the Gowri references with Copp, to arrive at the claimed methods of administering a 5-lipoxygenase inhibitor to a human subject to treat elevated serum triglycerides. Read in their entirety, the Gowri references actually discourage from substituting any lipoxygenase inhibitor since the references had mixed success with the lipoxygenase inhibitors tested. In particular, Gowri 2000 showed that esculetin, another lipoxygenase inhibitor, had no anti-lipolytic activity in rats. Gowri 1999 only showed an effect on rat blood pressure after treatment with masoprocol. Gowri 1999 did not test any other lipoxygenase inhibitors. At most, Gowri 1999 was an invitation for further research, and Gowri 2000 subsequently complicated the implications of the role of lipoxygenase inhibitors in lipolytic activity by providing mixed results with the lipoxygenase inhibitors tested.

Moreover, Copp does not rectify the shortcomings of Gowri 1999 and Gowri 2000. The mere disclosure of a single lipoxygenase inhibitor lowering blood pressure and lipolytic activity in rats, followed by disclosure that another lipoxygenase inhibitor does not have the expected effect in lowering lipolytic activity, provides no indication that it would necessarily be successful to use a phenyl pyrazoline derivative (or any other lipoxygenase inhibitor, for that matter) in the treatment of hypertension or elevated serum triglycerides in a human subject. As such, for at least this reason, Appellants respectfully request this rejection be withdrawn.

4. The Examiner Has Not Established a Correlation Between Lipoxygenase Activity and Lowering of Serum Triglycerides.

The Examiner asserted that "Applicant in his remarks argues that the examiner has made the improper determination of masoprocol's status as a lipoxygenase inhibitor. However, applicant fails to establish that such a compound does not have lipoxygenase activity and the lowering of serum triglycerides and hypertension is not as a result of the inhibitory activity of the compound on the lipoxygenase pathway." Office Action mailed July 10, 2008, p. 2, lns. 10-13. Contrary to the Examiner's assertion, the burden is not on Applicants to show that masoprocol does not have lipoxygenase inhibitory activity; rather, the burden is on the Examiner to show that there is a correlation between 5-lipoxygenase inhibitory activity and the lowering of serum triglycerides. The Examiner must do this without relying on any teaching from the specification, as it is not proper to use information from the specification to establish a *prima facie* case of obviousness.

In order to prevent obviousness rejections based on hindsight analysis, the Federal Circuit has explained that even after *KSR* a flexible approach to the teaching-suggestion-motivation test remains the primary guarantor against the use of improper hindsight in establishing a rejection based on obviousness. *See Ortho-McNeil Pharmaceuticals, Inc. v Mylan Laboratories, Inc.* 520 F.3d 1358, 1364-1365, 86 U.S.P.Q.2d 1196, 1201 (Fed. Cir. 2008). It is recognized that the teaching, suggestion or motivation need not always be found in the writing but may be found within the knowledge and creativity of the ordinary artisan. *Id.* at 1365, U.S.P.Q.2d at 1201. Appellants assert that without looking at the present specification, there would be no reason to think that a phenyl pyrazoline derivative would be effective at lowering serum triglyceride levels. This is especially true since it was known at the time the invention

was made that classification as a 5-lipoxygenase inhibitor was not necessarily predictive of a lowering serum triglyceride effect. For example, esculetin is a 5-lipoxygenase inhibitor that does not lower serum triglyceride levels. *See* Gowri 2000 at p. E599, col. 2, lns. 4-5. Thus, a serum triglyceride lowering effect is not predictably associated with 5-lipoxygenase activity.

The Examiner further alleged that "in view of the prior art and based on KSR a person skilled in the art would have been motivated to try and use a compound having lipoxygenase activity inhibitory activity for the treatment of elevated serum triglycerides or hypertension." Office Action mailed July 10, 2008, p. 2, lns. 16-19. Appellants respectfully disagree with this position.

The present application is drawn to methods of treating elevated serum triglyceride levels by the administration of a pharmaceutical composition comprising a 5-lipoxygenase inhibitor. The enzyme 5-lipoxygenase converts arachidonic acid to 5-hyrdoxyperoxyeicosatetraenoic acid (5-HPETE). *See, e.g.*, p. 7, lns. 6-7 of the specification. There is no indication in the art, or based on the general knowledge of the ordinary artisan, that the 5-lipoxygenase enzyme is involved in the synthesis of triglycerides. The 5-lipoxygenase enzyme also does not play a role in release or absorption of triglycerides in and out of the blood stream into tissues where the fatty acids may be stored or used for energy. *See, e.g.*, Pulliger, C.R. and Kane, J.P. "Lipid metabolism and transport," in *Molecular Biology and Biotechnology*, Meyers R.A. ed., VCH Publishers New York, pp. 494-501 (1995), specifically Figures 1 and 2 submitted hereto as Exhibit 6). Thus, the ordinary artisan would *not* have reasonably looked to administer a 5-lipoxygenase inhibitor in order to lower triglyceride levels in the serum of a patient.

In addition, the Examiner has not established that it is the 5-lipoxygenase inhibitory activity of masoprocol that is responsible for the anti-lipolytic effect in the treated subject. The Gowri references describe using masoprocol *in vivo*, and both observe that masoprocol has anti-lipolytic activity associated with the compound. However, anti-lipolytic activity is not the only activity associated with masoprocol, as masoprocol possesses many physiological activities including lipoxygenase inhibition, antioxidant activity, and dephosphorylating hormone sensitive lipase (HSL). *See, e.g.,* Gowri 2000, p. E593, Abstract. Thus, the cited references do not establish that it is the 5-lipoxygenase inhibitory activity that causes the lowering of the serum triglyceride levels.

In particular, in Gowri 2000 it is asserted that

> [t]he antilipolytic activity effect of masoprocol on isolated adipocytes was associated with a fall in HSL activity, and by using an anti phosphoserine antibody, we were able to show that this loss in activity was associated with a decrease in the phosphorylated state of HSL. This confirms that masoprocol may be stimulating a serine/threonine phosphatase via a second messenger pathway and may be causing dephosphorylation of HSL.

Gowri 2000, p. E599, left col., lns. 47-55. The phosphorylated form of HSL is the active form, and the active form converts the cellular triglyceride stored in adipocytes into free fatty acids and glycerol. The anti-lipolytic activity may be associated with an interaction between the inhibitor and hormone sensitive lipase and not between the inhibitor and 5-lipoxygenase. In fact, in view of masoprocol's numerous physiological activities, it is likely that the serum lowering effect of masoprocol is due to the dephosphorylation of HSL and not the effect on lipoxygenase. Thus, the correlation between the 5-lipoxygenase inhibitory activity and the serum triglyceride lowering activity has not been established. Without this correlation the ordinary artisan could not reasonably predict that a 5-lipoxygenase inhibitor would be effective at lowering serum triglyceride levels.

As such, for at least this reason, Appellants respectfully request this rejection be withdrawn.

5. Masoprocol as the Lead Compound Would Not Direct the Ordinary Artisan to a Phenyl Pyrazoline Derivative as a Compound For Triglyceride Lowering Activity.

A *prima facie* case obviousness involving structurally similar compounds requires a showing that there is adequate support in the prior art for the changing of the structure of a compound. *See Takeda Chemical Industries v. Alphapharm*, 492 F.3d 1350, 1356, 83 U.S.P.Q.2d 1169, 1174 (Fed. Cir. 2007), citing *In re Grabiak*, 769 F.2d 729, 731-732, 226 U.S.P.Q. 870, 873 (Fed. Cir. 1985). "Normally a prima facie case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound." *Takeda* 492 F.3d at 1356, 226 U.S.P.Q. at 873 citing *In re Deuel*, 51 F.3d 1552, 1558, 34 U.S.P.Q.2d 1210, 1215 (Fed. Cir. 1995). There is the additional requirement that the "prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention." *Id.* citing *In re Jones*, 958 F.2d 347, 351, 21 U.S.P.Q.2d 1941, 1944 (Fed. Cir. 1992); *In re Dillon*, 919 F.2d 688, 692, 16 U.S.P.Q.2d 1897, 1901 (Fed. Cir. 1990); *In re Grabiak*, 769 F.2d 729, 731-32, 226 U.S.P.Q. 870, 872 (Fed. Cir. 1985); *In re Lalu*, 747 F.2d 703, 705, 223 U.S.P.Q. 1257, 1258 (Fed. Cir. 1984). The court held that in "cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish a prima facie case of obviousness of a new claimed compound." *Takeda*, 492 F.3d at 1357, 83 U.S.P.Q. 2d at 1175. Thus, the holding in *Takeda* provides that a *prima facie* case of obviousness requires the identification of a lead compound in the references followed by a clear articulation of the reasons why the artisan would change the compound in a particular way to achieve a predictable result.

Here, the compounds of the cited art are not structurally similar to the compounds of the claims. *See, e.g.*, Structure Comparison of Lipoxygenase Inhibitors submitted hereto as Exhibit 7. Even assuming, *arguendo*, the ordinary artisan would choose masoprocol or curcumin as the lead compound, there is nothing in the art that would lead the ordinary artisan to modify either compound in such a way that the ordinary artisan would arrive at a phenyl pyrazoline derivative structure.

Furthermore, the Gowri references do not show that lipoxygenase inhibitors, acting through the 5-lipoxygenase pathway, act to lower serum triglycerides. The speculative nature of the Gowri references in linking the lipoxygenase pathway to masoprocol's observed effects and the observation of another (non-phenyl pyrazoline derivative) lipoxygenase inhibitor (esculetin) not having the same anti-lipolytic properties that masoprocol has would certainly not rise to the level of providing predictability and motivating one skilled in the art to substitute one lipoxygenase inhibitor for another lipoxygenase, especially in view of the divergent structures.

Thus, there is no reason for the ordinary artisan to choose a phenyl pyrazoline derivative in methods of lowering serum triglyceride levels. As such, for at least this reason, Appellants respectfully request this rejection be withdrawn.

6. The Record Provides Evidence of Unexpected Results, Which Must Be Considered By the Office.

Secondary considerations of non-obviousness include unexpected results, commercial success, long-felt need, failure of others, licensing by competitors, copying, initial skepticism and later praise by experts, and near simultaneous invention by others. *Graham v. John Deere Co.*, 383 U.S. 1, 17, 86 S. Ct. 684, 694, 148 U.S.P.Q. 459, 467 (1966). The Federal Circuit has recently reaffirmed that the USPTO must in all cases consider any evidence presented by Appellants tending to support secondary

considerations of non-obviousness. *In re John B. Sullivan and Findlay E. Russell*, 498 F.3d 1345, 84 U.S.P.Q.2d 1034 (Fed. Cir. 2007).

As discussed above, the Examiner has not established a *prima facie* case of obviousness with respect to any of claims 1, 4, 5, 8, 9 or 14-17. Moreover, the record clearly demonstrates that *prima facie* obviousness, even if it were established, would be wholly negated by the unexpected properties of the claimed invention, namely, the inventors' discovery of a means to reduce elevated serum triglyceride levels using 5-lipoxygenase inhibitors.

As described in the specification, masoprocol (nordihydroguaiaretic acid or NDCA) and curcumin exhibit multiple biological properties, including lipoxygenase inhibition, and exhibit hypolipidemic effects. *See, e.g.,* p. 1, ln. 11- p. 2, ln. 7 of the specification. However, as discussed above, there was uncertainty in the art regarding whether these hypolipidemic effects were caused by lipoxygenase inhibition, and specifically, the art did not attribute these effects to the inhibition of 5-lipoxygenase. *See id.* and also Exhibits 1-2 and 4-5. Moreover, it was known in the art that masoprocol and curcumin are poorly bioavailable agents and thus, must be administered in prohibitive and possibly toxic concentrations. *See, e.g.*, p. 2, lns. 10-11. As such, the present inventors fulfilled a need in the art for a new means to reduce elevated serum triglyceride levels using certain bioavailable 5-lipoxygenase inhibitors.

In addition, the specification provides detailed experimental results showing *in vivo* efficacy of 5-lipoxygenase inhibitors in animal models of hypertriglyceridemia. For example, Figure 1 shows treatment with 4,5-dihydro-1-(3-(trifluoromethyl)phenyl)-1H-pyrazol-3-amine (BW-755c), a phenyl pyrazoline derivative, resulted in a significant decrease in serum triglycerides in rats fed a high fructose diet. *See, e.g.,* Figure 1, "BW-

755c 100 mg/kg bid," Figure 2B, top panel "BW-755c-5" and p. 18, ln. 23- p. 19, ln. 2 of the specification. In view of the uncertainty in the art regarding the mechanism of the hypolipidemic properties of masoprocol and curcumin, and the absence of a teaching or suggestion in the art that these properties related to the inhibition of 5-lipoxygenase, the effectiveness of 5-lipoxygenase inhibitors in treating elevated triglyceride serum levels would have been unexpected at the time of the present invention. As such, for at least this reason, Appellants respectfully request this rejection be withdrawn.

7. Conclusion

For at least the reasons discussed above, Appellants respectfully submit that the Examiner has not established a *prima facie* case of obviousness with respect to any of claims 1, 4, 5, 8, 9 or 14-17. Moreover, the record clearly demonstrates that *prima facie* obviousness, even if it were established, would be wholly negated by the unexpected properties of the claimed invention. Therefore, the rejection of claims 1, 4, 5, 8, 9 and 14-17 under 35 U.S.C. § 103(a) should be reversed, and the claims be allowed to issue.

v. Claim 9 Is Not Obvious Over the Cited Art.

Claim 9, which depends indirectly from claim 1, differs from claim 1 in that it further specifies that the 5-lipoxygenase inhibitor is 4,5-dihydro-1-(3-(trifluoromethyl)phenyl)-1H-pyrazol-3-amine (BW 755c), a phenyl pyrazoline derivative. For at least the reasons stated above, plus the *additional* requirement that the 5-lipoxygenase inhibitor is BW 755c, claim 9 must be found to be non-obvious over the references cited by the Examiner.

vi. Claims 16 and 17 Are Not Obvious Over the Cited Art.

Claims 16 and 17, which depend directly or indirectly from claim 1, differ from claim 1 in that they further specify the administration of a second compound selected from the group consisting of anti-diabetic compounds, lipid-lowering medications and anti-hypertensive compounds (claim 16), or concurrent administration of a second compound selected from the group consisting of anti-diabetic compounds, lipid-lowering medications and anti-hypertensive compounds (claim 17), respectively. For at least the reasons stated above, plus the *additional* requirement of a second compound selected from the group consisting of anti-diabetic compounds, lipid-lowering medications and anti-hypertensive compounds (claim 16), or concurrent administration of a second compound selected from the group consisting of anti-diabetic compounds, lipid-lowering medications and anti-hypertensive compounds, claims 16 and 17 must be found to be non-obvious over the references cited by the Examiner.

vii. Claims 5 and 8 Are Independently Not Obvious Over the Cited Art.

Claims 5 and 8, which depend directly or indirectly from claim 1, differ from claim 1 in that they specify the 5-lipoxygenase inhibitor is selected from the group consisting of an acetohydroxamic acid derivative, a phenyl pyrazoline derivative, a 2-(12-hydroxydodeca-5,10-diynyl)-3,5,6-trimethyl-1,4-benzoquinone derivative, and a 3-[1-(4-chlorobenzyl)-3-t-butyl-thio-5-isopropylindol-2-yl]-2,2-dimethyl propanoic acid derivative (claim 5), or the 5-lipoxygenase inhibitor is a phenyl pyrazoline derivative (claim 8), respectively. As discussed above, Appellants have addressed the claims in this Appeal Brief to the extent that the Examiner has examined the elected species of phenyl pyrazoline derivatives. However, Appellants assert that claims 5 and 8, although not separately addressed by the Examiner in view of the examination of the elected species,

must be found to be non-obvious over the references cited by the Examiner for at least the reasons above, plus the *additional* requirements of claim 5 and 8.

viii. Summary

Based on the factual findings set forth in detail herein, and further in view of USPTO guidance and well-settled case law, Appellants respectfully conclude that, in view of the differences between the cited art as a whole and the presently claimed invention as a whole, a person of ordinary skill in the art would have never predictably arrived at the claimed invention. In particular, Appellants assert that:

(a) the Examiner has not articulated with particularity the reasons to support the finding that one skilled in the art would have substituted one element for another and has merely presented a conclusory statement without providing any evidence that masoprocol only acts as a lipoxygenase inhibitor and has *no* other physiological effects, contrary to the teaching in Gowri 2000;

(b) a person of ordinary skill in the art would not have found the claimed invention predictable, especially in view of the observation that not all lipoxygenase inhibitors have anti-lipolytic activity;

(c) there is no reasonable expectation of success in combining the Gowri references with Copp to arrive at the claimed invention, since the Gowri references had mixed success with lipoxygenase inhibitors tested thereby discouraging the ordinary artisan from combing the references directed to different types of lipoxygenase inhibitors;

(d) the Examiner bears the burden to show that the cited art shows a correlation between lipoxygenase activity and the lowering of serum triglycerides and has not met this burden; and

(e) due to the structural differences between masoprocol and phenyl pyrazoline derivatives, an ordinary artisan would not be directed to phenyl pyrazoline derivatives as a lead compound for triglyceride lowering activity.

Accordingly, under the Supreme Court's obviousness jurisprudence established in *Graham* and reaffirmed in *KSR*, and under USPTO Guidelines, the Examiner has failed to establish a *prima facie* case of obviousness of any of claims 1, 4, 5, 8, 9 or 14-17. For at least the reasons stated above, plus the additional requirements of claims 5, 8, 9, 16 and 17, including rebuttal evidence of unexpected results if *prima facie* obviousness was established, Appellants respectfully request that the rejection of claims 1, 4, 5, 8, 9 and 14-17 under 35 U.S.C. § 103(a) as being unpatentable over Gowri 1999 and Gowri 2000 in view of Copp be reversed, and that the claims be allowed to issue.

Respectfully submitted,

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VIII. Claims Appendix (37 C.F.R. § 41.37(c)(1)(viii))

1. A method for treating elevated serum triglycerides comprising administering to a human subject with elevated serum triglycerides an effective amount of pharmaceutical composition comprising a 5-lipoxygenase inhibitor, said effective amount being sufficient to reduce said elevated serum triglycerides, wherein said 5-lipoxygenase inhibitor is not nordihydroguaiaretic acid (NDGA) or curcumin.

4. The method of claim 1, wherein the pharmaceutical composition is an oral dosage form.

5. The method of claim 1, wherein said 5-lipoxygenase inhibitor is selected from the group consisting of an acetohydroxamic acid derivative, a phenyl pyrazoline derivative, a 2-(12-hydroxydodeca-5,10-diynyl)-3,5,6-trimethyl-1,4-benzoquinone derivative, and a 3-[1-(4-chlorobenzyl)-3-t-butyl-thio-5-isopropylindol-2-yl]-2,2-dimethyl propanoic acid derivative.

8. The method of claim 5, wherein said 5-lipoxygenase inhibitor is a phenyl pyrazoline derivative.

9. The method of claim 8, wherein said phenyl pyrazoline derivative is 4,5-dihydro-1-(3-(trifluoromethyl)phenyl)-1H-pyrazol-3-amine (BW 755c).

14. The method of claim 1, wherein said effective amount of said 5-lipoxygenase inhibitor is between 0.1 μg and 500 mg per kilogram of body weight.

15. The method of claim 14, wherein said effective amount of said 5-lipoxygenase inhibitor is between 0.5 mg to 500 mg per kilogram of body weight.

16. The method according to claim 1, further comprising administering a second compound selected from the group consisting of anti-diabetic compounds, lipid-lowering medications and anti-hyptertensive [*sic*, hypertensive] compounds.

17. The method according to claim 14 [*sic*, claim 16], wherein the 5-lipoxygenase inhibitor and said second compound are administered concurrently.

IX. Evidence Appendix (37 C.F.R. § 41.37(c)(1)(ix))

Copies of the evidence relied upon by Appellants in this Appeal Brief are provided. The Table below sets forth the location of the evidence in the Record.

Exhibit	Title of Exhibit	Location in Record
Exhibit 1	Gowri *et al.*, *Am. J. Hypertens.* 12: 744-746 (1999).	Cited as Document AR4 by Applicants in an IDS dated March 15, 2004. Cited by the Examiner in the Office Action mailed January 9, 2008.
Exhibit 2	Gowri *et al.*, *Am. J. Physiol. Endocrinol. Metab.* 279: E593-E600 (2000).	Cited as Document AS4 by Applicants in an IDS dated March 15, 2004. Cited by the Examiner in the Office Action mailed January 9, 2008.
Exhibit 3	U.S. Patent No. 4,572,913 to Copp *et al.*	Cited by the Examiner in the Office Action mailed January 9, 2008.
Exhibit 4	Scribner *et al.*, *Metabolism* 49(9): 1106-1110 (2000).	Cited as Document AT10 by Applicants in an IDS dated March 15, 2004.
Exhibit 5	U.S. Patent No. 6,191,169 B1 to Nadler *et al.*	Cited as Document AE3 by Applicants in an IDS dated March 15, 2004.
Exhibit 6	Pulliger, C.R. and Kane, J.P. "Lipid metabolism and transport," in *Molecular Biology and Biotechnology*, Meyers R.A. ed., VCH Publishers New York, pp.494-501 (1995), specifically Figures 1 and 2	Submitted as Exhibit A in Applicants' Amendment and Reply Under 37 C.F.R. 1.116 dated September 10, 2008.
Exhibit 7	Structure Comparison of Lipoxygenase Inhibitors	Submitted as Exhibit B in Applicants' Amendment and Reply Under 37 C.F.R. 1.116 dated September 10, 2008.

X. Related Proceedings Appendix (37 C.F.R. § 41.37(c)(1)(x))

[None]